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A new and objective definition of the term "indefinite survival" in organ transplantation in the animal model

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Dear Editors:

The ultimate goal in transplantation is life-long survival of the transplanted organ without immune suppression, also known as "indefinite survival". Intensive study has been undertaken to achieve immune tolerance specific to the donor, and encouraging results have been reported [2]. Unfortunately, in animal studies there is remarkable controversy concerning the length of rejection-free time after which survival may be called "indefinite". Actually, in the literature there is no clear definition of this term. The objective of this letter is to discuss which duration of survival is required, to be called "indefinite", and to present a formula for estimating this period.

For this article, the literature on transplantation studies in rat and mice models was searched for the term "indefinite survival". In total, 66 articles published between 1970 and March 2001 were reviewed. Regardless of the type of transplanted organ, the average rejection-free time defined as constituting indefinite survival ranged between 63 and 701 days in rats and between 60 and 300 days in mice (Table 1). Overall, cardiac transplantation was the most commonly performed procedure.

The term "indefinite survival" actually defines a certain period after which survival of the organ is accepted as "life-long". It does not mean that the use of the term is justified merely if the graft has not yet been rejected when an animal dies. After all, the transplantation may have been performed on an older subject that has already completed most of its expected life period, resulting in too short a follow-up in any case. For this reason there ought to be a standardized rejection-free period specific to each species for comparison of results. Otherwise, it would be impossible to compare the efficiency of immune tolerance methods. In addition, it should be emphasized that the standardization of the signs of rejection alone is not adequate to discuss the success rate of immune tolerance unless the description of survival time is clarified.

Unfortunately, there is no precise criterion to estimate or dictate the length of follow-up. One solution could be to apply human data to animal models. Per definition, an organ surviving indefinitely should be functional during the normal life span of the subject after transplantation. This period can be formulated as:

$$\begin{aligned} &\text{IDST} = \text{ALH} - \text{AAT} \\ &\text{IDST}: \text{ indefinite survival time} \\ &\text{ALH}: \text{ average life expectancy in humans} \\ &\text{AAT}: \text{ average age at time of transplantation in humans} \end{aligned} \quad (1)$$

Table 1 Shortest and longest survival times reported as "indefinite" for each type of transplantation procedure

Animal	Organ	Range in days [reference]
Rats	Heart	77 [10]–365 [17]
	Kidney	63 [15]–200 [8]
	Islet cells	150 [12]–180 [14]
	Small bowel	100 [4]–400 [9]
	Hind limb	200 [1]–360 [7]
	Skin graft	100 [19]–150 [18]
Mice	Heart	100 [11]–150 [3]
	Skin graft	< 60 [13]–300 [5]
	Islet cells	100 [16]–200 [6]

Since the average age of patient is different in organ transplantation, this should also be taken into account for the estimation of IDST in the animal model. A coefficient to estimate the length of period equal to life duration in humans can easily be found with this equation:

$$C = ALA/ALH \quad (2)$$

C : coefficient
ALA : average life expectancy in the animal
ALH : average life expectancy in humans

Equation 1 can be used in the animal model by simply multiplying by "C":

$$IDST(A) = (ALH - AAT) \times C \quad (3)$$

IDST(A): indefinite survival time in the animal model
ALH: average life expectancy in humans
AAT: average age at time of transplantation in humans
C: coefficient

If we put Eq. 2 in the place of C in Eq. 3 and make final adjustments, we get:

$$IDST(A) = (ALH - AAT) \times (ALA/ALH) \quad (4)$$

For example, if we assume that the research subject is kidney transplantation and that the animal has an average life expectancy of 3 years, and if we accept ALH to be roughly 70 years and AAT to be 40 years, "indefinite survival time" in this animal model would be:

$$\begin{aligned} IDST(A) &= (70 - 40) \times (3/70) \text{ years} \\ &= 30 \times 0.04 \text{ years} \\ &= 1.2 \text{ years} \end{aligned} \quad (5)$$

In the case of cardiac transplantation in the same animal model, if we assume AAT to be 55 years, IDST (A) would be 0.6 years.This formula is open to modification based on physiological aging of the animal model and time of chronic rejection in each organ. Nevertheless, "indefinite survival" should be based on objective criteria, and with this approach, standardization of and, eventually, consensus on the term "indefinite survival time" might be obtained.

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